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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,586	12/20/2001	Vanessa Chisholm	P1746R1	1705
9157 7590 09/28/2009 GENENTECH, INC. 1 DNA WAY SOUTH SAN FRANCISCO, CA 94080				
EXAMINER				
SGAGLAS, MAGDALENE K				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/019,586

Applicant(s)

CHISHOLM ET AL.

Examiner

Magdalene K. Sgagias

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 151 and 153-160 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 151, 153-160 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's arguments filed 7/30/09 have been fully considered. The amendment has been entered. Claims 1-150 are canceled.

Claims 151, 153-160 are pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 113-115 under 35 U.S.C. 103(a) as being unpatentable over Lucas (Nucleic acid Research, 24(9): 1774-1779, 1996 (IDS)); Crowley (US 5,561,053 (IDS) in view of Mosser et al, Biotechnology 22:150-154, 1997 (IDS) is withdrawn.

Claims **151, 153-160** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Crowley** (US 5,561,053 (IDS) in view of **Liu et al** (WO/1995/024485, published 09/14/1995, IDS); **Mosser et al**, Biotechnology 22:150-154, 1997 (IDS); **Bennett et al** (BioTechniques, 24(3): 478-482, 1998 (IDS); **Tan et al**, (US 6,235,967; see whole document; hereinafter the '967 patent (IDS); **Chishima et al**, (Cancer Res. 1997; 57:2042-47 (IDS).;

Crowley teaches a method of obtaining a cell expressing a desired product, the method comprising: **a)** introducing into mammalian cells a vector comprising: **(i)** a single transcription

unit comprising a promoter, an intron positioned 3' to the promoter and a polynucleotide encoding the desired product positioned to the intron; (ii) a polynucleotide encoding an amplifiable selectable marker dihydrofolate reductase (DHFR), wherein the intron is defined by a 5' splice donor site and a 3' splice acceptor site such that the efficiency of splicing messenger RNA having said splice donor sequence is between 80% and 99% as determined by quantitative PCR, and a 3' acceptor site; and wherein the polynucleotide encoding the desired product and the promoter are operably linked to the polynucleotide encoding the DHFR selectable marker; b) isolating the cells by culturing the cells under conditions that preferentially allow for the growth or survival of those cells that synthesize the DHFR selectable marker encoded by the selectable gene, wherein expression of the DHFR amplifiable selectable marker is indicative of the cell expressing the desired product; and c) recovering said desired product from said cells (columns 53-54, figures 1A-1D, and example 1-3). Crowley discloses the selectable gene is positioned within an intron defined by a splice donor site and a splice acceptor site and the selectable gene and product gene are under the transcriptional control of a single transcriptional regulatory region (abstract) (claims 151, 159-160). Crowley teaches that the DHFR is the most widely used amplifiable gene which encodes a dihydrofolate reductase enzyme (column 2 bridge to column 3). The selection agent used in conjunction with a DHFR gene is methotrexate (Mtx). A host cell is cotransfected with a product gene encoding a desired protein and a DHFR gene, and transfectants are identified by first culturing the cells in culture medium that contains Mtx (column 2 bridge to column 3) (claims 156, 158). Crowley discloses the transfected cells are cultured so as to express the gene encoding the product in a selective medium comprising an amplifying agent for sufficient time to allow amplification to occur, whereupon either the desired product is recovered or cells having multiple copies of the product gene are identified (abstract). Crowley discloses protein expression is measured using

ELISA and the product of interest preferably is recovered from the culture medium as a secreted polypeptide, (column 17, lines 41-46) and purify the product of interest from recombinant cell proteins or polypeptides to obtain the product of interest for example, by fractionation on immunoaffinity (column 17, lines 46-63). Crowley differs from the present invention for not teaching a second transcription unit comprising a second promoter and an intron positioned 3' of the second promoter; and a polynucleotide encoding a green fluorescent protein (GFP).

However, at the time of the instant invention was made **Liu et al** teach a polynucleotide construct that induces the co- expression of three gene products, wherein the construct has a first eukaryotic promoter operatively linked to a first cistron, and a second cistron operatively controlled by its own promoter, and a third cistron downstream of the second cistron, operatively controlled by a third promoter, further containing a transcriptional terminator following each of the first, second and third cistron (see claim 1 of '485). It is also disclosed that the coordinate expression results in improved expression of the exogenous gene products which maybe otherwise poorly expressed in a single cell (see page 1 of '485). Additionally, Liu et al teach that direction of transcription by various promoters and the genes they control are in opposite directions (see page 19, lines 30-35). Liu et al indicates that vector modification and development procedures may be accomplished according to methods known in the art (see page 14, last line to page 15, lines 1-14). Liu et al teach that the DNA construct may use any known eukaryotic promoter including immunoglobulin promoter and polyadenylation terminator. Liu et al also disclose SV40 promoter and SV40 polyA in the construct. In a preferred embodiment, Liu et al teach use of CMV promoter and BGH polyA (page 4, line 23, and page 14, lines 14-15). Liu teaches multiple constructs, for example encoding gp 160, gp120, gp41 . or any other HIV gene may be prepared, mixed and co-administered and protein expression is maintained following DNA injection and standard techniques of molecular biology for preparing

and purifying DNA constructs enable the preparation for example of DNA immunogens of this invention (p 34-35). Although Liu et al teach a nucleic acid construct comprising (a) a nucleotide sequence that encodes a first polypeptide operably linked to first promoter and a first polyadenylation signal; (b) a second transcriptional unit comprising a nucleotide sequence that encodes a second polypeptide operably linked to a second promoter and a second polyadenylation signal; (c) a third transcriptional unit comprising a nucleotide sequence that encodes a third polypeptide operably linked to a third promoter and a third polyadenylation signal, but differed from the claimed invention by not explicitly teaching use of the polynucleotide encoding a green fluorescence protein GFP in a transcriptional unit.

However, prior to instant invention the GFP selectable marker in dicistronic expression cassette was known in the art in a transcriptional unit. For instance, **Mosser et al** teach the use of plasmid containing a dicistronic expression cassette encoding GFP and a target gene, in a method of screening and selection of cells expressing inducible genes (p 152-153). Mosser suggests the dicistronic GFP plasmid can be used for identifying clones that stably express a tTA-regulated gene product and also to identify those cells that express a protein of interest following a transient transfection (p 154, 1st column). Mosser does not disclose the GFP for FACS sorting.

However, prior to instant invention use of GFP for cell sorting was known to one of ordinary of skill in the art. For instance, **Bennett et al** (BioTechniques, 24(3): 478-482, 1998) teaches that it is routine in the art to fuse GFP selectable marker with the Zeocin-resistance marker for the identification and selection of transfected mammalian cells (abstract). Bennett reaches the GFP selectable marker provides a way to determine transient transfection efficiencies in tissue culture cells using fluorescence activated cell sorting (FACS) analysis (abstract, and p 482, 1st column). Expression of the GFP-ZeoR was also used to identify and

select stable mammalian cell lines expressing a heterologous gene (abstract). Selection was efficient and GFP fluorescence provides an excellent, noninvasive technique to monitor the success of Zeocin selection during the development of the stable cell lines (abstract). Bennett suggests that FACS could be used for sorting cell populations with high or low levels of heterologous gene expression and to identify cell lines that overexpress therapeutic protein for purification (p 482, 1st column). Bennett teaches because plasmids are integrated as a single cassette, it is reasonable to assume that insertion at a transcriptionally active site that results in high-level expression of the fluorescent selectable marker would also have high expression of the heterologous gene (p 482, 1st column). **Tan et al** teaches in the '967 patent teaches a polynucleotide where GFP is fused to a selected sequence (e.g. methioninase or T antigen) and operably linked to a promoter. (e.g. Abstract; Fig. 1a). Furthermore, GFP can be of a higher fluorescence mutated (i.e. S65T) variety. (e.g. col. 3, 1. 26). In addition, various cell types can be transfected with the polynucleotide, including methotrexate selected CHO cells. (e.g. col. 3, line 63, col. 6, 11.27-37). Furthermore, the '967 indicates using a DHFR-GFP dicistronic vector (e.g. col. 6, Example 1; showing GFP-S65T mobilization into pED-mtx resistant) and explicitly teaches that such vector systems can be used to express proteins in mammalian cells. (e.g. col. 9, 11.40-45). The '967 patent doesn't expressly provide a construct where a target gene is operably linked to either a gene encoding GFP or a gene encoding an amplifiable selectable marker, where the construct comprises both genes regardless. Furthermore, the '967 patent teaches that a dicistronic vector comprising both a fluorescence encoding gene (i.e. GFP) and an amplifiable selectable marker (i.e. DHFR) can be used. (e.g. col. 9, II. 40-45). In addition, the '967 patent teaches that said polynucleotides can be used for production of a fusion protein (e.g. GFP-T antigen). (e.g. col. 9, II. 50-51). Therefore, the '967 patent provides the motivation to construct a vector comprising a gene encoding a fluorescence marker, an amplifiable

selectable marker and a target protein. In addition, Chishima et al. teach an expression construct where a GFP gene (S65T) is mobilized into a dicistronic expression vector comprising an amplifiable gene (i.e. DHFR) and a gene expressing a desired product. (Chishima, at 2042, col. 2, ¶3, referring to the pED-mtx resistant construct described in, Kaufman et al. Nucleic Acids Research. 1991, 19(16):4485-90) (Note: this second reference is only being cited to provide information with regard to intrinsic properties of the pED-mtx resistant expression construct not as additional art, See MPEP § 2131.01). Kaufman et al. teach that the pED-mtx resistant construct contains a gene encoding a desired product operably linked to a promoter (i.e. B-lactamase gene, Kaufman, at 4487, Fig. 1). Chishima et al. further teach that the construct replicates in CHO cells. (Chishima, at 2042, col. 2, ¶4).

Therefore, it would have been well within the knowledge of one of ordinary of skill to construct the expression vector to produce the GFP fusion proteins as contemplated by the '967 patent. The ordinary skilled artisan, seeking to develop a construct for expressing proteins that can be easily be monitored via fluorescence and that can be selected for in mammalian cells via amplifiable markers such as DHFR, would have been motivated to incorporate the teachings of the '967 patent or Chishima et al. to construct a expression construct comprising GFP, a selected sequence and DHFR, operably linked to a promoter. It would have been obvious for the ordinary skilled artisan to so construct an expression vector and transfect mammalian cells to express the desired fusion proteins. Furthermore, given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said artisan would have had a reasonable expectation of success in practicing the claimed invention. It would have been prima facie obvious for a person of ordinary of skill in the art seeking to develop a vector with two transcriptional units for isolating cells and purifying the product of interest to combine the respective teachings of Liu taken with Mosser and

Bennett by introducing a second transcriptional unit into the first transcriptional unit of Crowley for a coordinated expression of the amplified DHFR marker and the selectable GFP marker in a mammalian cell with a reasonable expectation of success. A person of skill in the art would have been motivated to introduce a second transcriptional unit as taught by the Liu/Mosser/Bennet to the DHFR transcriptional unit of Crowley as a matter of design of choice amounting to combining prior art elements according to known methods as taught by Liu to yield predictable results. Additionally, given Liu tech direction of transcription by various promoters and the genes they control it would have been obvious for one of ordinary of skill in the art to combine the DHFR and the GFP transcriptional units in order to culture cells in MTX so as to express the gene encoding the product in a selective medium comprising MTX the amplifying agent for sufficient time to allow amplification to occur, whereupon either the desired product is recovered or cells having multiple copies of the product gene are identified as taught by Crowley and particularly since Liu teaches that the coordinate expression of genes in a vector with two transcriptional units results in improved expression of the exogenous gene products which maybe otherwise poorly expressed in a single cell. Moreover, one of ordinary of skill in the art would have been particularly motivated to combine the two transcriptional units since Bennett teaches that GFP fused to a resistance marker integrated as a single cassette, it is reasonable to assume that insertion at a transcriptionally active site that results in high-level expression of the fluorescent selectable marker would also have high expression of the heterologous gene.

With respect to limitations directed to isolating cells expressing the GFP comprising sorting for and cloning the brightest 1%-10% of fluorescent cells by FACS analysis, it must be noted that where a prior art product teaches the limitation of sorting cells by GFP fluorescence using a FACS cell sorter, the percentage of fluorescent cells by FACS analysis is a property that is considered intrinsic to FACS cell sorting for which is not something that the Office can determine. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See *in re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). In this case the difference at issue would be GFP FACS sorting and cloning of GFP fluorescent cells in the prior art and the claimed GFP comprising sorting for and cloning the brightest 1%-10% of fluorescent cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR International Co. v. Teleflex Inc.* (KSR), 550 U.S. at, 82 USPQ2d at 1395. Thus, the claimed invention as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Obviousness Type Double Patenting Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 113-127, 130, 132-137, 140-151 and 163-164 provisional rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-58 of copending Application No. 11/535,038 (hereafter the '038 application) is withdrawn.

Claims 113-127, 130, 132-137, 140-151 and 163-164 provisional rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-58 of copending Application No. 11/535,003 is withdrawn.

Claims -127, 130, 132-137, 140-151 and 163-164 **rejection** directed to an invention not patentably distinct from claims 1-58 of commonly assigned application 11/535,003 is withdrawn.

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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